Notice of Allowability	Application No.	Applicant(s)	
	09/751,053	GIL ET AL.	
	Examiner	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *RESPONSE FILED 01/2004*.
2. ☒ The allowed claim(s) is/are *1-21,23-28,30-44 and 68-71*.
3. ☒ The drawings filed on *12/29/2000* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
8. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the margin according to 37 CFR 1.121(d).
9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No. _____
4☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5☐ Notice of Informal Patent Application (PTO-152)
6☐ Interview Summary (PTO-413), Paper No._____ .
7☐ Examiner's Amendment/Comment
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other

JEZIA RILEY
PRIMARY EXAMINER

ALLOWED CLAIMS/ TJ

1. (Amended) An agent comprising:

a therapeutic component, and

a targeting ligand coupled to the therapeutic component, the targeting ligand being effective to bind to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s).

(Original)

2. An agent according to claim 1 wherein the therapeutic component interferes with the release of neurotransmitters from a cell or its processes.

(Original)

3. An agent according to claim 2 wherein the therapeutic component comprises a light chain component.

4. (Amended) An agent according to claim 2 wherein the light chain component comprises a light chain or a fragment thereof of a botulinum toxin, a butyricum toxin, a tetani toxin or biologically active variants thereof.

5. (Amended) An agent according to claim 2 wherein the light chain component comprises a light chain or a fragment thereof of a botulinum toxin type A, B, C1, D, E, F, G or biologically active variants thereof.

6. (Amended) An agent according to claim 2 wherein the light chain component comprises a light chain or a fragment thereof of a botulinum toxin type A or biologically active variants thereof.

(Original)

7. An agent according to claim 1 wherein the therapeutic component inactivates cellular ribosomes.

(Original)

8. An agent according to claim 7 wherein the therapeutic component is saporin.

(Original)

9. An agent according to claim 1 which further comprises a translocation component.

(Original)

10. An agent according to claim 9 wherein the translocation component facilitates the transfer of at least a part of the agent into the cytoplasm of the target cell.

(Original)

11. An agent according to claim 9 wherein the translocation component facilitates the transfer of the therapeutic component into the cytoplasm of the target cell.

(Original)

12. An agent according to claim 9 wherein the translocation component comprises a heavy chain component.

13. (Amended) An agent according to claim 12 wherein the heavy chain component comprises a heavy chain or a fragment thereof of a botulinum toxin, a butyricum toxin, a tetani toxin or biologically active variants thereof.

14. (Amended) An agent according to claim 12 wherein the heavy chain component comprises a heavy chain or a fragment thereof of a botulinum toxin type A, B, C1, D, E, F, G or biologically active variants thereof.

15. (Amended) An agent according to claim 12 wherein the heavy chain component comprises a heavy chain or a fragment thereof of a botulinum toxin type A or biologically active variants thereof.

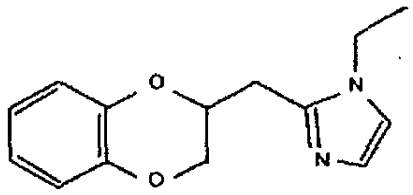
16. (Amended) An agent according to claim 15 wherein the fragment of the heavy chain comprises at least a portion of the amino terminal fragment of the heavy chain.

(Original)

17. An agent according to claim 1 wherein the therapeutic component comprises a light chain of a botulinum toxin type A and the translocation component comprises a fragment of a heavy chain of a botulinum toxin type A, wherein the fragment of a heavy chain can assist in the translocation of at least the therapeutic component into a cytoplasm of a cell.

(Original)

18. An agent according to claim 1 wherein the targeting component is represented by the formula:

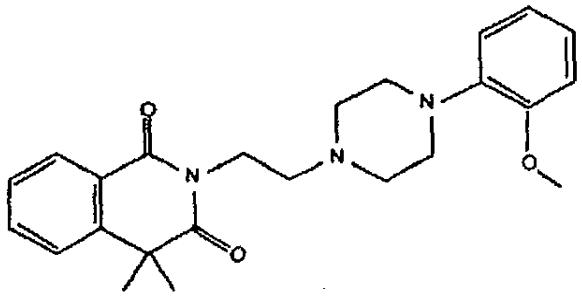


Imiloxan

I.

(Original)

19. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:

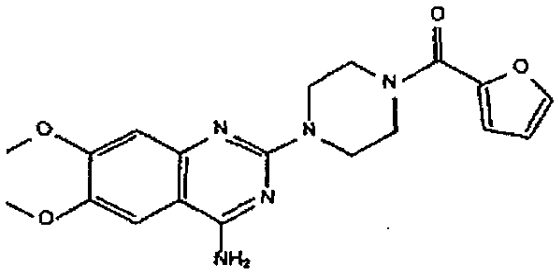


ARC 239

II.

(Original)

20. An agent according to claim 1 wherein the targeting component is a compound represented by the formula

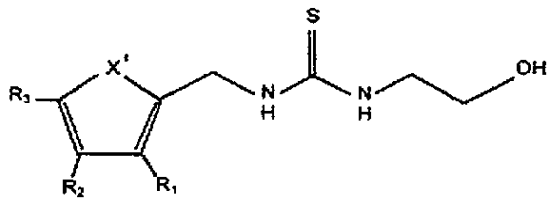


Prazosin

III.

(Original)

21. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:



IV.

wherein X' is selected from the group consisting of R_4-C=C-R_5 and R_4-C;

a six membered carbon ring structure is formed when X' is R_4-C=C-R_5;

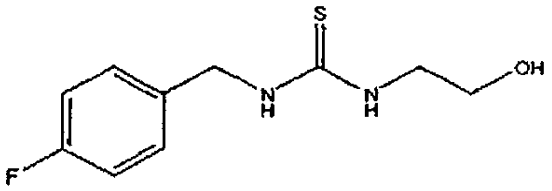
a five membered carbon ring is formed when X' is R_4-C;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of F, Cl, Br, I, OR_6 and H, wherein R_6 is H or an alkyl, including a methyl, an ethyl or a propyl.

Cancel Claim 22

(Original)

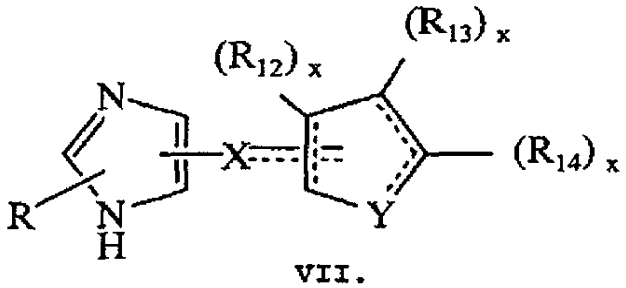
23. An agent according to claim 1 wherein the targeting component is a compound represented by the formula:



VI.

(Original)

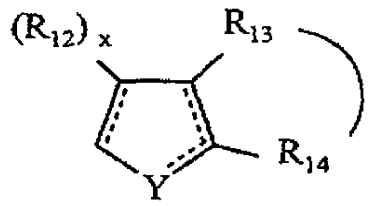
24. An agent according to claim 1 wherein the targeting component is represented by the formula



VII.

wherein the dotted lines represent optional double bonds; R is H or lower alkyl; X is S or $C(H)R_{11}$, wherein R_{11} is H or lower alkyl or R_{11} is absent when X is S or when the bond between X and the ring represented by

is a double bond; Y is O, N, S, $(C(R_{11})X)_y$, wherein y is an integer of from 1 to 3, -CH=CH- or $-Y_1CH_2-$, wherein Y_1 is O, N or S; x is an integer of 1 or 2, wherein x is 1 when R_{12}, R_{13} or R_{14} is bound to an unsaturated carbon atom and x is 2 when R_{12}, R_{13} or R_{14} is bonded to a saturated carbon atom; R_{12} is H, lower alkyl, halogen, hydroxy, lower alkoxy, lower alkenyl, acyl or lower alkynyl or, when attached to a saturated carbon atom, R_{12} may be oxo; R_{13} and R_{14} are, each, H, lower alkyl, halogen, lower alkenyl, acyl or lower alkynyl, or, when attached to a saturated carbon atom, R_{12} may be oxo; R_{13} and R_{14} are, each, H, lower alkyl, halogen, lower alkenyl, acyl, lower alkynyl, aryl, heteroaryl, or substituted aryl or heteroaryl, wherein said substituent is halogen, lower alkyl, lower alkoxy, lower alkenyl, acyl, lower alkynyl, nitro, cyano, trifluoromethyl, hydroxy, or phenyl or, together, are $-(C(R_2)x)z-$; $-Y_1(C(R_2)x)z'-$; $-Y_1(C(R_2)x)yY_1-$; $-(C(R_2)x)-Y_1-(C(R_2)x)-$; $-(C(R_2)x)-Y_1-(C(R_2)x)-(C(R_2)x)-$ and $-Y_1-(C(R_2)x)-Y_1-(C(R_2)x)-$ wherein z is an integer of from 3 to 5, z' is an integer of from 2 to 4 and x and y are as defined above, and further either end of each of these divalent moieties may attach at either R_{13} or R_{14} to form the condensed ring structure



and the ring thus formed may be totally unsaturated, partially unsaturated, or totally saturated provided that

a ring carbon has no more than 4 valences, nitrogen no more than three and O and S have no more than two.

(Original)

25. An agent according to claim 1 wherein the targeting component comprises an amino acid component.

(Original)

26. An agent according to claim 25 wherein the amino acid component is an antibody.

(Original)

27. An agent according to claim 26 wherein the antibody is raised from an antigen component, the antigen component comprises a second extracellular loop of an alpha-2B receptor.

(Original)

28. An agent according to claim 27 wherein the second extracellular loop is conjugated to a keyhole limpet hemocyanin.

Cancel Claim 29

(Original)

30. An agent according to claim 25 wherein the amino acid component comprises a variant peptide, a variant polypeptide, a variant protein or a variant protein complex of a wild type peptide, polypeptide, protein or protein complex, respectively.

(Original)

31. An agent according to claim 25 wherein the amino acid component is a variant polypeptide.

(Original)

32. An agent according to claim 31 wherein the variant polypeptide is a variant heavy chain.

(Original)

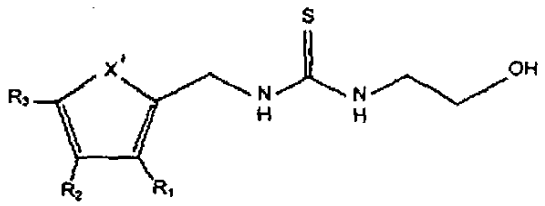
33. An agent according to claim 1 wherein the therapeutic component and the targeting component are attached to each other through a spacer component.

(Original)

34. An agent according to claim 9 wherein the therapeutic component, the translocation component and the targeting component are attached to each other through a spacer component.

(Original)

35. An agent according to claim 34 wherein the therapeutic component is a light chain of a botulinum toxin type A, the translocation component is a fragment of a heavy chain of a botulinum toxin type A which can facilitate the translocation of at least the light chain into a cytoplasm of a cell, and the targeting component is represented by the formula:



IV.

wherein X' is selected from the group consisting of R_4-C=C-R_5 and R_4-C;

a six membered carbon ring structure is formed when X' is R_4-C=C-R_5;

a five membered carbon ring is formed when X' is R_4-C;

R_1, R_2, R_3, R_4 and R_5 are each independently selected from the group consisting of F, Cl, Br, I, OR_6 and H, wherein R_6 is H or an alkyl, including a methyl, an ethyl or a propyl.

(Original)

36. An agent according to claim 34 wherein the spacer component comprises a moiety selected from the group consisting of a hydrocarbon, a polypeptide other than an immunoglobulin hinge region, and a proline-containing polypeptide identical or analogous to an immunoglobulin hinge region.

(Original)

37. An agent according to claim 1 useful for treating chronic pain in a mammal, including a human.

(Original)

38. An agent according to claim 37 wherein the chronic pain is treated without substantially affecting acute pain sensation or tactile sensation.

39. (Amended) A method for making an agent for treating pain comprising the step of producing a polypeptide from a gene having codes for at least one component of the agent, wherein the agent comprises

a therapeutic component, and

a targeting ligand coupled to the therapeutic component, the targeting ligand being effective to bind to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s).

(Original)

40. A method for making an agent according to claim 39 wherein the agent further comprises a translocation component.

(Original)

41. A method according to claim 40 wherein the therapeutic component comprises a light chain of botulium toxin type A and the translocation component comprises a fragment of a heavy chain which is able to facilitate the transfer of at least the light chain into the cytoplasm of the target cell.

(Original)

42. A method according to claim 40 wherein the targeting component comprises an amino acid component.

(Original)

43. A method according to claim 42 wherein the amino acid component comprises a variant peptide, a variant polypeptide, a variant protein, or a variant protein complex of a wild type peptide, polypeptide, protein or protein complex.

(Original)

44. A method according to claim 43 wherein the variant peptide is a variant heavy chain.

Cancel Claims 45-67

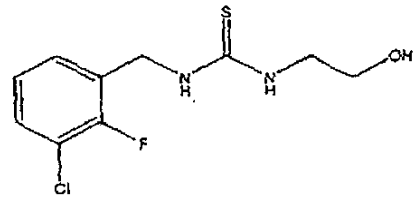
68. (New) The agent of claim 1, wherein the targeting ligand selectively binds to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.

69. (New) The method of claim 39, wherein the targeting ligand of the agent selectively binds to the alpha-2B or alpha-2B/alpha-2C adrenergic receptor subtype(s) as compared to the alpha-2A adrenergic receptor subtype.

70. (New) An agent comprising:

a therapeutic component, and

a targeting component coupled to the therapeutic component, the targeting component being represented by the formula:



V.

71. (New) An agent comprising:

a therapeutic component, and

a targeting component coupled to the therapeutic component, the targeting component comprising an antibody raised from an antigen component comprising a second extracellular loop, the second extracellular loop comprising an amino acid sequence of KGDQGPQPRGRPQCKLNQE (SEQ ID NO: 1).